REMARKS

Claims 1-21 are pending in this application. Claims 1-11, 15-17 and 19-21 have been canceled. Claims 12 and 18 have been amended. No new matter has been added by this amendment. A Declaration is attached herewith to further clarify the invention. Reconsideration is respectfully requested in light of the following remarks and amendments.

Applicants are pleased to acknowledge the withdrawal of objections to claims 12 and 18. Applicants are further pleased to acknowledge the withdrawal of the 35 U.S.C. §112, second paragraph rejection. The provisional rejection of claims 12-14 and 18 under 35 U.S.C. 101 for double patenting with claims 11-13 and 17 of application 09/622,568 is being held in abeyance since both applications are pending.

I. Rejection of Claims 12-14 and 18 under 35 U.S.C. §112, first paragraph

The Examiner has maintained the rejection of claims 12-14 and 18 under 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these claims. The Examiner acknowledges that both prior art at the time of filing and the instant specification provide

sufficient teaching of a method of sensitizing human tumor cell lines to chemotherapeutic pro-drugs by inducing a vector encoding a relevant carboxylesterase (CE) to said cell lines *in vitro*. However, the Examiner has based the non-enablement rejection upon application of the method *in vivo*. The Examiner suggests that at the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the therapeutic protein had not been developed. Further, the Examiner suggests that expression of CE in tumor cells that are transfected *in vitro* is entirely different from a patient bearing a tumor in an *in vivo* setting. Finally, the Examiner suggests that one skilled in the art would require undue experimentation in order to determine which prodrug can be metabolized by a CE. Applicants respectfully disagree.

Contrary to the Examiner's suggestion that the success of gene therapy is unpredictable, the previously provided papers entitled "Gene Therapy of Human Severe Combined Immunodeficiency (SCID-1)-X1 disease", Science 288 (5466):669-672 (2000) and Khuri FR, et al., "A Controlled Trial of Intratumoral ONYX-015, a Selective-Replicating Adenovirus in Combination with Cisplatin and 5-fluorouracil in Patients with Recurrent Head and Neck Cancer",

Nature Medicine 6(8):879-885 (2000) show that at the time of filing the present application, the use of gene therapy was appreciated by one of skill in the art to have progressed to the point of being successful in humans. Also, Applicants respectfully point out on page 6, lines 28 through page 7, line 2 of the specification, a number of gene therapy clinical trials have demonstrated success. Further, as shown in the attached Table 1, numerous clinical trials have proven the effectiveness of gene therapy in cancer treatment. The observed measurable anti-tumoral responses of Phase I gene therapy studies are proof of predictable success. (See attached Declaration at Paragraph 12).

The Examiner has further suggested that sensitization of tumor cells to a mouse relies upon sufficient expression of CE in tumor cells that are transfected *in vitro*. The Examiner suggests that a mouse model is entirely different from a patient bearing a tumor in an *in vivo* setting. The Examiner still further suggests that the duration of expression of a desired protein by an adenoviral vector is short. Applicants respectfully disagree.

Section 2107.02 of the MPEP states "if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays or from testing in an animal model or a combination thereof almost invariably will be sufficient to

establish therapeutic or pharmacological utility for a compound, composition or process. Section 2107.02 of the MPEP further states "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use *Nelson v. Bowler,* 626 F.2d 853, 857, 206 USPA 881, 884 (CCPA 1980). Further as decided in *In re Brana,* 34 USPQ 2d, 1436 (CAFC 1995). Where tumor cell lines were implanted into mice, the tumor models were held to represent a specific disease.

The animal xenograft model described in the present application indicates that if sufficient CE levels can be achieved in tumor cells then regressions will occur following CPT-11 treatment *in vivo.* (See particularly Examples 8, 9, and 11 and see attached Declaration at Paragraph 3). The animal xenograft model teaches the potential usefulness of this class of prodrugs metabolizing carboxylesterases in humans, and more importantly fails to provide any reasonable basis to doubt that the pharmacological activity observed in cells and animal models in the

instant invention would also occur in cells, in animals and humans. (See specification at pages 25-31 and Examples 6-12, also see attached Declaration at Paragraphs 4-11).

In addition, the courts have held that it is only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility, does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See *In re Bundy,* 209 USPQ 48, 51 (CCPA 1981).

Applicants respectfully assert that the PTO has not satisfied its initial burden, and Applicants should not have to substantiate a presumptively correct disclosure to avoid a rejection under the first paragraph of section 112, as the mouse tumor model alone should be sufficient to satisfy Applicants' burden, as a matter of law.

Additionally, the duration of expression of the adenoviral vector as disclosed in Example 11 may be relatively short, however the Examiner has not provided any evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility of the vector. Further, as shown in Table 1, Phase I studies of patients using the adenoviral vector delivery have been proven to be successful. Additionally, short term high level

expression of CE is optimal for gene therapy with CPT-11, accordingly, viral vectors provide the most suitable delivery to achieve this level of *in vivo* gene delivery. (See attached Declaration at Paragraph 13). Intratumoral and intravenous administration of recombinant adenovirus are suitable delivery methods as supported throughout the application and at pages 16, and 41-42. (See attached Declaration at Paragraph 12). The dosage of the adenovirus needed to induce a tumor response, $5x10^9$ pfu (see attached Declaration at Paragraphs 7 and 10) is within the range of 10^6 to 10^{10} pfu taught in the specification as effective for intratumoral injection of adenovirus (see Example 11 and page 41, line 22 through page 42 line 12). In addition, the Heise et al. 1977 Nature Med. 3:639-645 reference recited on page 42 at line 7 describes the use of ONYX-015 vector which shows an anti-tumoral efficacy following intratumoral or intravenous administration to nude mouse-human tumor xenografts. The ONYX-713 vector used in the experiments described in Paragraphs 7-9 of the Declaration is identical to the ONYX-015 except that ONYX-713 contains CE whereas the ONYX-015 does not. Applicants respectfully request reconsideration.

Further, in an earnest attempt to facilitate the prosecution of this case, claim 12 has been amended to clarify that the CE is

capable of cleavage of an ester or carbamate linkage of a chemotherapeutic prodrug. This amendment is supported at page 30 lines 8-13, and throughout the specification. Further support is found at Figure 8, which shows the carbamate linkages found in CPT-11, SN-38 and APC.

Claim 18 has been amended to clarify that the composition may be administered intratumorally or intravenously as supported throughout the specification and especially at page 28 and Example 11.

Withdrawal of this rejection is respectfully requested.

II. Conclusion

Applicants believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a Declaration and a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made".

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Claims 1-11, 15-17 and 19-21 have been canceled.

Claims 12 and 18 have been amended as follows:

12. (twice amended) A method for sensitizing tumor cells to a chemotherapeutic prodrug comprising transfecting selected tumor cells with a composition comprising an isolated polynucleotide encoding a carboxylesterase capable of ~~metabolizing~~ the cleavage of an ester or carbamate linkage of a chemotherapeutic prodrug and inactive metabolites thereof to active drug, and a disease-specific responsive promoter wherein expression of the carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic prodrug.

18. (twice amended) A method of inhibiting tumor growth in a patient comprising administering to a patient a composition comprising an isolated polynucleotide encoding a carboxylesterase capable of metabolizing a chemotherapeutic prodrug and inactive metabolites thereof to active drug, a disease-specific responsive promoter, wherein the dosage of said composition is one determined to produce the longest delay of recurrent disease and wherein the composition is administered intratumorally or intravenously.